

# The Effect of Gabapentin on Liver Tissues and Enzymes in Rats

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## Abstract

**Introduction:** Gabapentin is a widely used anticonvulsant drug discovered in the 1970s in Japan it is synthesized by adding cyclohexyl group gamma-aminobutyric acid (GABA). Although Gabapentin is a well-tolerated drug and is widely used for treatment of post-herpetic pain, partial seizures, restless leg syndrome. Several cases reported that gabapentin might cause drug-induced hepatic injury in patients without co-existing cause of hepatic injury, and caused significant elevation in levels  $\gamma$ -glutamyl transpeptidase (GGT), alanine aminotransferase (ALT) and aspartate amino aspartate (AST) while internalized normalized ratio (INR), bilirubin levels, and alkaline phosphatase (ALP) levels were normal. Interestingly discontinuation of gabapentin treatment led to reversal of hepatocellular injury.

**Materials and methods:** Sixteen females randomly divided into two main groups (n=8), the negative control or (CN-Gr), which was fed usual nutrition and water Ad libitum for thirty days. The treatment or (Tre-Gr), which assigned as the Gabapentin (Brown & Burk UK Ltd (BBUK<sup>®</sup>) and was allowed for the free access to normal rat chow and a single daily dose by gavage of 1 mL/rat of (BBUK<sup>®</sup>) 400 mg/ kg of body weight, which was administered for 30 days

**Results:** Gabapentin treatment did not increase AST nor ALT; however, the serum ALP was significantly increased, hematological parameters were not affected by gabapentin treatment. Histopathological study showed evident congestion of central vein and congested of dilated sinusoid.

**Conclusion:** Even high doses of gabapentin (400mg/kg) for 30 days does not produce deleterious adverse effects on the liver nor the haematological parameters. Further investigation is required to investigate even higher doses of gabapentin for longer time.

**Keywords:** Enzymes in Rats, Liver Tissues, Hepatocellular Injury.

DOI: 10.47750/pnr.2022.13.S03.001

## INTRODUCTION

Gabapentin is a widely used anticonvulsant drug discovered in the 1970s in Japan it is synthesized by adding cyclohexyl group gamma-aminobutyric acid (GABA)<sup>(1,2)</sup>.

Gabapentin mode of action does not include direct activation of GABA pathway nor affect metabolism or uptake of GABA neurotransmitter. but it exerts its analgesic effect by unique effect on voltage-dependent Ca<sup>+2</sup> channels at the postsynaptic dorsal horns and thus interrupt the series of events that possibly leads to the experience of a neuropathic pain sensation<sup>(3)</sup>. Furthermore, Gabapentin exerts its anticonvulsant activity by selectively acting on neurons located on the outer layers of the cerebral cortex<sup>(4)</sup>.

Although Gabapentin is a well-tolerated drug and is widely used for treatment of postherpetic pain, partial seizures, restless leg syndrome and other off-label treatment like bipolar disorder, fibromyalgia, headache and postmenopausal hot flushes. Its use does not lack of some serious adverse effects and they were dose dependent<sup>(2,3)</sup>.

Several cases reported that gabapentin might cause drug-

induced hepatic injury in patients without co-existing cause of hepatic injury, and caused significant elevation in levels  $\gamma$ -glutamyl transpeptidase (GGT), alanine aminotransferase (ALT) and aspartate amino aspartate (AST) while internalized normalized ratio (INR), bilirubin levels, and alkaline phosphatase (ALP) levels were normal. Interestingly discontinuation of gabapentin treatment led to reversal of hepatocellular injury<sup>(5,6)</sup>.

Richardson et al. in 2002 reported that gabapentin induces cholestasis in 50 years old patient received a 900 mg of gabapentin for two weeks. Clinical findings showed that gabapentin led to significant elevation of liver enzymes (ALT, AST, and GGT) and bilirubin levels while other causes of viral hepatitis were excluded<sup>(7)</sup>.

A study carried in 2020 to show the effect of Gabapentin (at a dose of 300mg/day for one month) on liver histology of rats and showed no serious effects in the histology of liver, pancreas and spleen, however it showed that few lymphocyte infiltrations occurred in the tissue of the liver<sup>(8)</sup>. On the other hand, a previous study showed that administration of Gabapentin intraperitoneally (20 or 100 mg/kg) for 45 days.

They found minute foci of necrosis in occurred in the liver parenchymal cells of some rats treated with high dose of gabapentin (100mg/kg). Whereas, at therapeutic dose (20mg/kg) no significant changes were found in the histopathology and biochemical indices of the liver (as compared to control group). The serum levels of ALT, AST ALP, lactate dehydrogenase, total bilirubin and direct bilirubin were enhanced significantly with 100 mg/kg. Interestingly albumin and total protein decreased (in 100 mg/kg group) as compared to the control group<sup>(9)</sup>.

Furthermore, it has been reported that patient received gabapentin for the management of neuropathic pain after 5 weeks of treatment the patient suffered from neutropenic sepsis the report said that neutropenia is rare adverse effect of associated with gabapentin treatment<sup>(10)</sup>.

Interestingly another study used mice to determine the effect of gabapentin on haematological parameters they showed 8 weeks of oral treatment with gabapentin (1 mg/kg) significantly decreased WBC count, RBC, MCH, and MCV as compared with the control group<sup>(11)</sup>. this effect is attributed to the effect of high dose of gabapentin on oxidative stress<sup>(11)</sup>.

Therefore, this study is aimed to demonstrate the effect of gabapentin (at a dose of 100 mg/kg orally for 30 days) on liver tissues and enzymes.

## MATERIALS & METHODS

### Animals & Housing

Mature female Wistar rats (*Rattus norvegicus*) (80 days old and weighing about 200 g) were obtained from the house of research and Experimental, University of Baghdad, College of pharmacy, where they were born and bred. The animals were housed under standard laboratory conditions, with a 12h light/12h dark photoperiod. They were fed on rat chow pellets and received water *ad libitum*. The experimental protocol was approved by the Ethical Committee of the College of pharmacy, University of Baghdad.

### Treatment Procedure

Sixteen females randomly divided into two main groups (n=8), the negative control or (CN-Gr), which was fed usual nutrition and water *Ad libitum* for thirty days. The treatment or (Tre-Gr), which assigned as the Gabapentin (Brown & Burk UK Ltd (BBUK<sup>®</sup>) and was allowed for the free access to normal rat chow and a single daily dose by gavage of 1 mL/rat of (BBUK<sup>®</sup>) 400 mg/ kg of body weight, which was administered for 30 days. During the experiments, the animals were observed twice daily for any abnormal clinical signs. Body weight was recorded before the beginning of treatment, at weekly intervals and at the end of 30 days treatment. Food ingestion was monitored daily.

The animals of the control group (CN-GR), and treatment group (Tre-GR), were euthanized by inhalation of an anesthetic (diethyl ether) on the 30rd day. Whole blood was collected from heart for serum biochemical analyses. Immediately after death, the livers were dissected out, and then fixed in buffered formalin for histological examination. To conduct a light microscope examination, the tissues were dehydrated in a graded series of ethanol, embedded in paraffin and sectioned at 5  $\mu$ m thickness for routine haematoxylin and eosin staining (Humason 1972).

### Statistical Analysis

Data were analysed using Statistical Package for the Social Sciences (SPSS, Version 25, Chicago, USA). Data presented as mean $\pm$ SEM. The comparison of different parameters and significance between treatment and control groups was performed using independent T-test with probability value of  $p < 0.05$  considered to be significant.

## RESULTS

### 1. Effect of Gabapentin treatment on Total serum Bilirubin (TSB)

There was no significant difference between treated and control ( $0.5 \pm 0.056$  vs  $0.5125 \pm 0.069$ ,  $p > 0.05$ ).

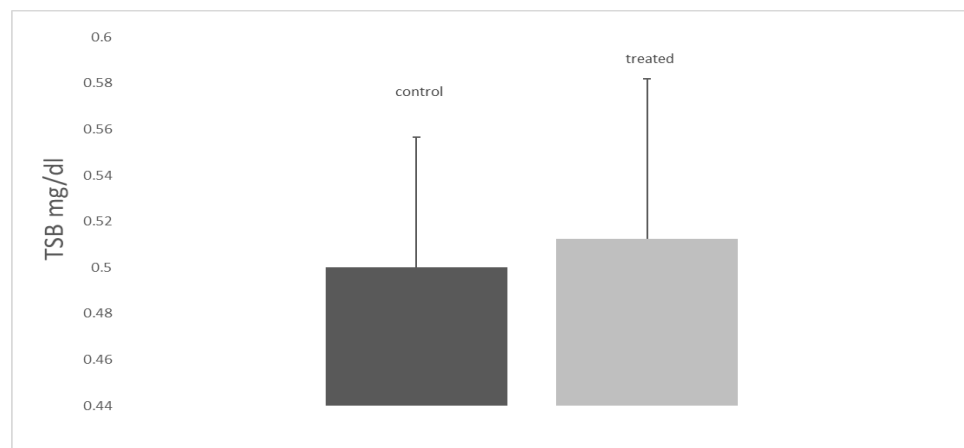


Figure 1: effect of gabapentin treatment of TSB. There was no significant effect of gabapentin treatment on TSB,  $p > 0.05$

2. Effect of gabapentin treatment on liver enzymes GPT(ALT), GOT (AST) and ALK(ALP):  
 There were no significant differences in GPT and GOT between control and treated groups ( $92.3 \pm 6.608$  vs  $68.74 \pm 16.36$ ,  $p > 0.05$ ) ( $159.2 \pm 29$  vs  $120.9 \pm 18.1$ ,  $p > 0.05$ ) respectively.

Interestingly gabapentin treatment significantly increased ALP as compared to the control group ( $67.23 \pm 23$  vs  $37.45 \pm 5.16$ ,  $p < 0.05$ ).

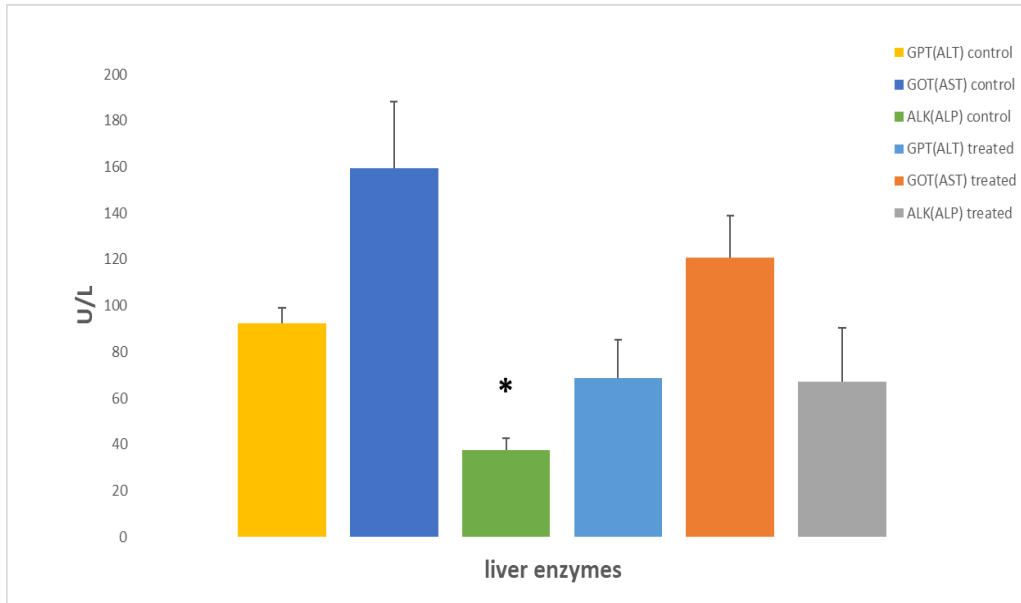


Figure 2: Effect of gabapentin treatment on liver enzymes, there were no significant in GPT, GOT difference between treated, and control group. However, ALK was significantly elevated in Gabapentin-treated group  $p < 0.05$

3. Effect of gabapentin on complete blood count (CBC)  
 Gabapentin treatment did not significantly affect any of CBC parameters as compared with control group.  $P > 0.05$ . Figures 3 and 4.

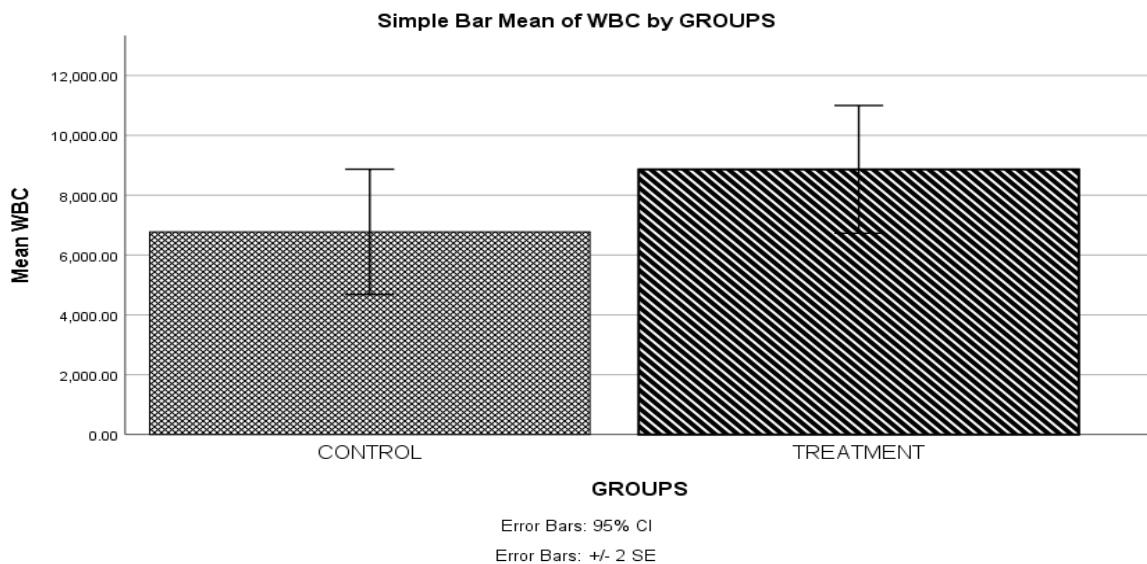


Figure-3 effect of gabapentin treatment on white blood cell count, no significant difference in WBC between control and treated group ( $6775 \pm 1045.9$  vs  $8862.5 \pm 1066.5$ ,  $p > 0.05$ ) respectively.

Other parameters are shown in figure-4,5, 6 and 7

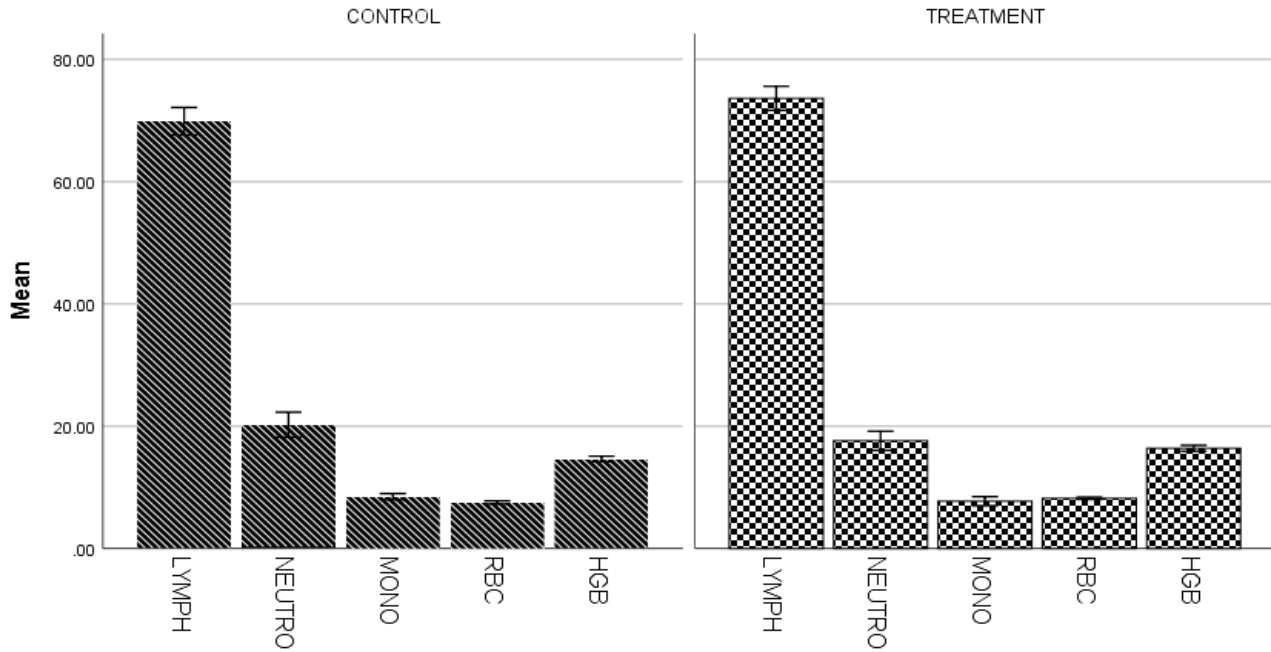


Figure-4: gabapentin treatment did not alter lymphocyte, neutrophils, monocytes, RBC and haemoglobin ( $73.63 \pm 1.96$  vs  $69.87 \pm 2.25$ ,  $20.25 \pm 2.04$  vs  $17.65 \pm 1.5$ ,  $8.5 \pm 0.5$  vs  $7.75 \pm 0.75$ ,  $8.25 \pm 0.18$  vs  $7.53 \pm 0.26$ ,  $16.4 \pm 0.5$  vs  $14.65 \pm 0.45$ ,  $p > 0.05$ ) respectively as compared to the control group.

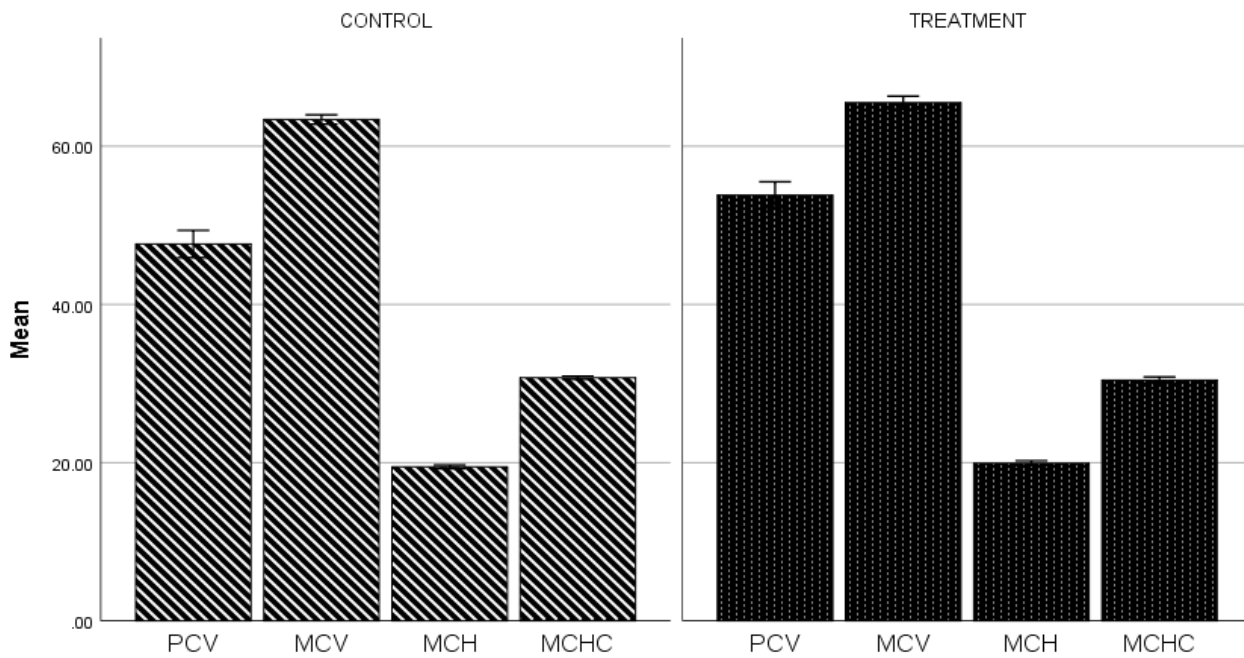


Figure-5: gabapentin treatment did not significantly affect packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin (MCHC) ( $53.8 \pm 1.07$  vs  $47.64 \pm 1.72$ ,  $65.51 \pm 0.813$  vs  $63.38 \pm 0.59$ ,  $19.94 \pm 0.313$  vs  $16.62 \pm 0.232$  and  $30.5 \pm 0.39$  vs  $30.74 \pm 0.2$ ,  $p > 0.05$ ) respectively as compared to control group.

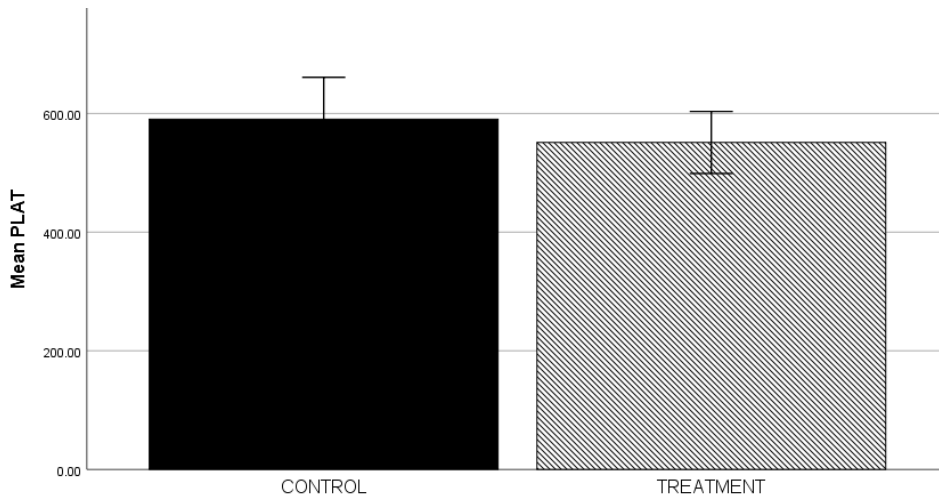


Figure-6: gabapentin treatment did not affect platelets count ( $551 \pm 26.14$  vs  $590.5 \pm 35.2$ ,  $p > 0.05$ ) as compared with control group.

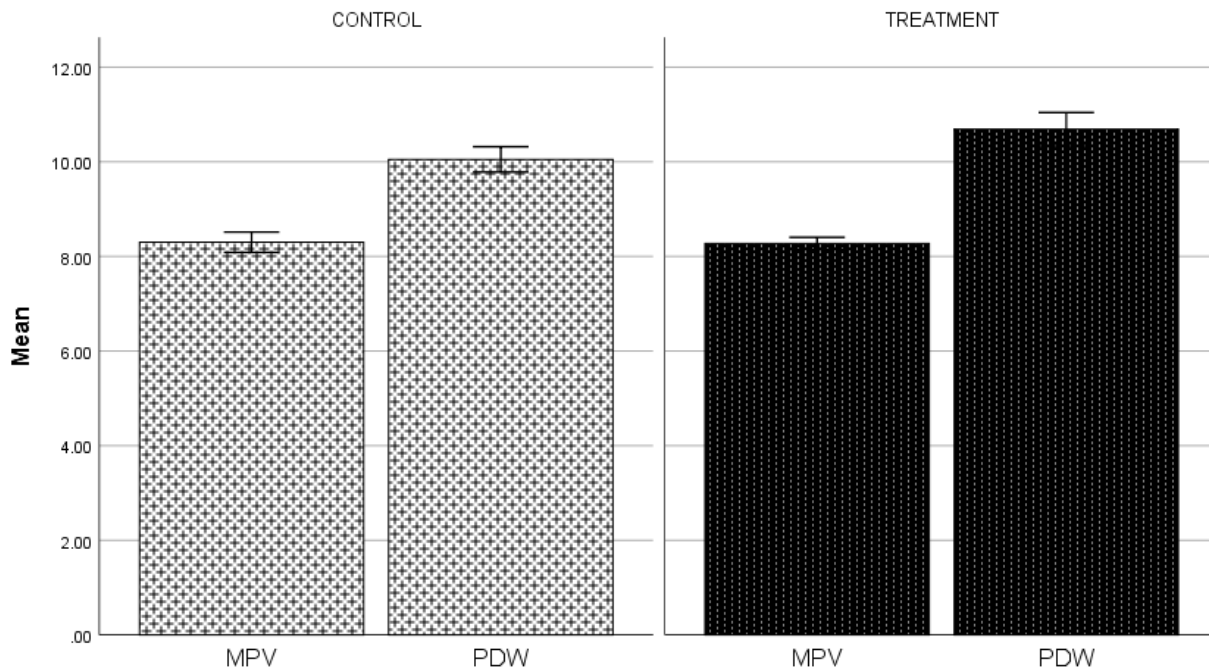
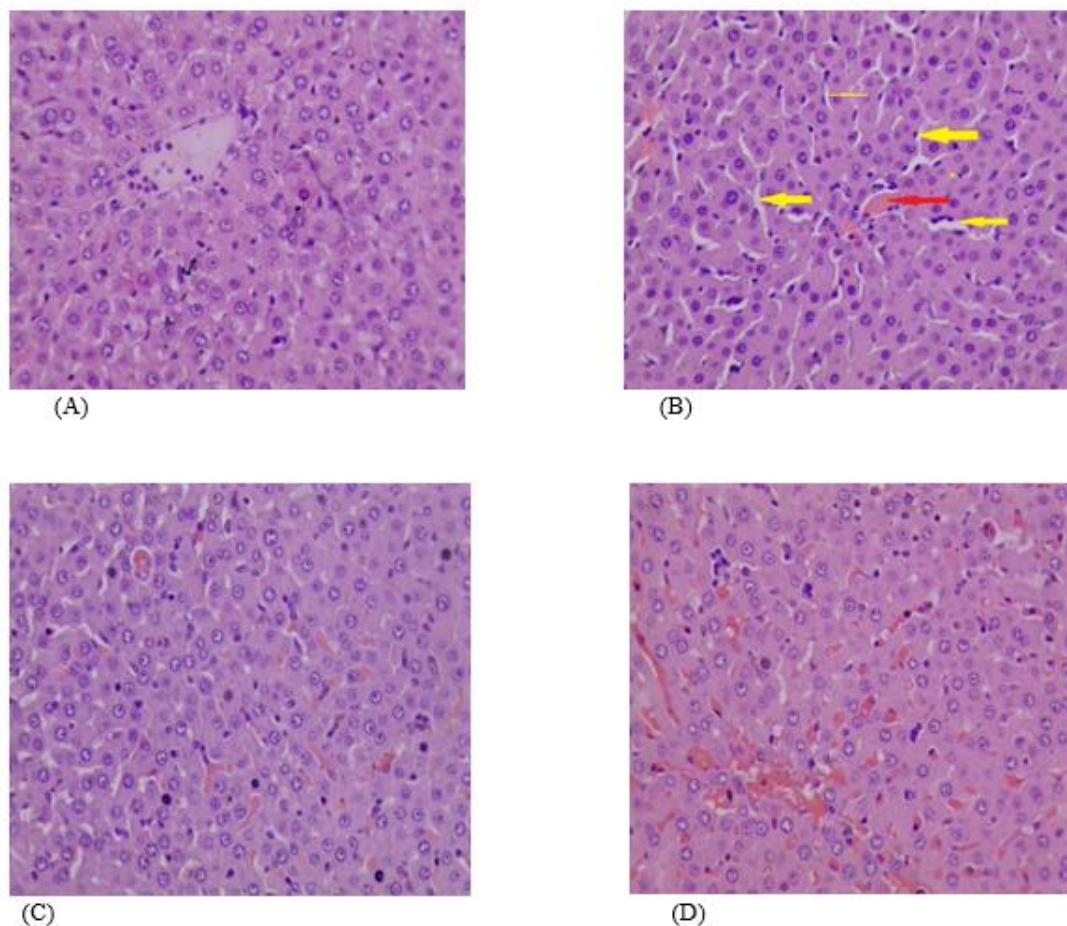


Figure-7: Gabapentin treatment did not affect mean platelet volume (MPV) ( $8.275 \pm 0.129$  vs  $8.3 \pm 0.215$ ,  $p > 0.05$ ) nor platelet distribution width (PDW) ( $10.69 \pm 0.35$  vs  $10.05 \pm 0.269$ ,  $p > 0.05$ ) as compared to the control group.

4. Effect of gabapentin on Histology of the Live tissue
  1. Control: Photo: A: Section showing normal histological structure appearance of hepatic tissue. (H & E) (X40).
  2. Photo: B: Showing preserve architecture of hepatic tissue with congestion and slight dilatation of sinusoid. (H & E) (X40).
  3. Photo: C: Section showing preserve architecture of hepatic tissue but with slight congested of dilated sinusoid. (H & E) (X40).
  4. Photo: D: Showing evident congestion of central vein and congested of dilated sinusoid. (H & E) (X40).



## DISCUSSION

Gabapentin is an analogue of gamma amino butyric acid, its mechanism of action is not fully understood. FDA granted approval for gabapentin for treatment of post-herpetic neuritis and epilepsy also used for management of pain associated with diabetic neuropathy (an-off label use). Gabapentin has a good bioavailability and it is highly protein bound; it is not metabolized in the liver appreciably and excreted in urine as unchanged drug however gabapentin-induced liver injury has been reported<sup>(12)</sup>. Liver injury caused by drug administration accounts for 10% of acute hepatitis per annum<sup>(5)</sup>.

In this study gabapentin treatment (400mg/kg) did not affect total serum bilirubin level while Meshkibaf et al found there was significant effect on total serum bilirubin when at gabapentin dose of 100mg/kg<sup>(9)</sup> while 20mg/kg has no effect on total serum bilirubin. Several case reports showed that bilirubin remains either normal or slightly elevated in cases of gabapentin-induced hepatitis (13, 14, 15 and 16).

Gabapentin treatment 400mg/kg did not significantly alter liver enzymes (GOT and GPT). Interestingly at this dose gabapentin treatment, significantly increased ALP enzyme as compared with control group. ALP enzymes are a group of isoenzymes, located on the outer layer of the cell membrane; they catalyze the hydrolysis of organic phosphate esters present in the extracellular space. Zinc and magnesium are important co-factors of this enzyme. ALP elevated level without elevation of other hepatic enzymes is usually associated with cholestatic liver disease<sup>(17)</sup>. Therefore, gabapentin treatment may have led to an obstruction of the biliary system.

Other findings gabapentin treatment did not significantly affect any of the CBC parameters while Al-Zahid et al found that 8 weeks of oral treatment with gabapentin (1 mg/kg) significantly decreased WBC count, RBC, MCH, and MCV as compared with the control group<sup>(11)</sup>. Moreover, they assumed this effect attributed to the effect of high dose of gabapentin on oxidative stress<sup>(11)</sup>. Interestingly case report showed that reversible thrombocytopenia occurs in HIV

patient after initiation of gabapentin treatment<sup>(18)</sup>.

The histopathological analysis of the hepatic tissues showed that gabapentin 400mg/kg caused no effect on the architectural changes on hepatic tissue but caused mild tissue congestion with slight dilatation of sinusoid in two samples while the last sample showed evident congestion of central vein and congested of dilated sinusoid. This effect is similar to other studies.<sup>(11)</sup>

Data are available about hepatotoxicity of gabapentin is limited. During clinical trials in epilepsy and diabetic neuropathy, treatment with gabapentin was not associated with an increased frequency of liver toxicity or serum aminotransferase elevations. Sporadic case reports have been published about hepatic injury resulted from gabapentin treatment, even though the underlying mechanism by which gabapentin induce liver injury was not always clear.<sup>(19)</sup> this attributed to the fact that gabapentin excretion is via renal pathway and has minimal metabolism in the liver and few cases of gabapentin-induced hepatotoxicity were reported<sup>(19,5)</sup>.

Therefore, this study suggests that even high doses of gabapentin (400mg/kg) for 30 days does not produce deleterious adverse effects on the liver nor the haematological parameters. Further investigation is required to investigate even higher doses of gabapentin for longer time.

## CONFLICT OF INTEREST

There is no conflict of interest.

## REFERENCES

- Yasaei R, Katta S, Saadabadi A. Gabapentin. [Updated 2020 May 24]. In: Stat Pearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2021 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK493228/>
- Taylor CP. Mechanisms of action of gabapentin. *Rev Neurol (Paris)*. 1997; 153 Suppl., 1:S39-45. PMID: 9686247.
- Rose, M.A. and Kam, P.C.A. (2002), Gabapentin: pharmacology and its use in pain management. *Anaesthesia*, 57: 451-462. <https://doi.org/10.1046/j.0003-2409.2001.02399.x>
- Hill DR, Suman-Chauhan N, Woodruff GN. Localization of [3H] gabapentin to a novel site in rat brain: autoradiographic studies. *Eur J Pharmacol*. 1993 Feb 15; 244(3): 303-9. doi: 10.1016/0922-4106(93)90156-4. PMID: 8384571.
- Jackson CD, Clanahan MJ, Joglekar K, Decha-Umphai ST. Hold the Gaba: A Case of Gabapentin-induced Hepatotoxicity. *Cureus*. 2018;10(3):e2269. Published 2018 Mar 4. doi:10.7759/cureus.2269
- Lasso-de-la-Vega, Maria C PharmD1; Zapater, Pedro MD1; Such, Jose MD2,3; Perez-Mateo, Miguel MD2,3; Horga, Jose F MD1,3 Gabapentin-Associated Hepatotoxicity, *American Journal of Gastroenterology*; December 2001 - Volume 96 - Issue 12 - p 3460-3462 doi: 10.1111/j.1572-0241.2001.05357.x
- Richardson, Charles E et al. "Gabapentin induced cholestasis." *BMJ (Clinical research ed.)* vol. 325, 7365 (2002): 635. doi:10.1136/bmj.325.7365.635
- A Lzubaidy FM, Bash AA, Jasim R. Study the Effect of Gabapentin on the Histology of Some Organs of Male rats. *Systematic Reviews in Pharmacy*. 2020; 11(9):95-101.

- Meshkibaf, Mohammad Hassan et al. "Chronic effect of gabapentin on liver function in adult male rats." *Acta medica Iranica* vol. 51, 12 (2013): 830-3.
- Derbyshire E, Martin D. Neutropenia occurring after starting gabapentin for neuropathic pain. *Clin Oncol (R Coll Radiol)*. 2004 Dec; 16(8):575-6. doi: 10.1016/j.clon.2004.06.015. PMID: 15630852.
- Al-Zahid, Jinan Mohammad, et al. "Effects of Gabapentin Drug on Hematological Parameters and Histological Structures in Female Mice." *Systematic Reviews in Pharmacy* 11.12 (2020): 695-700.
- Neurontin food and drug administration. [Feb; 2018]; [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2009/020235s041,020882s028,021129s027lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020235s041,020882s028,021129s027lbl.pdf) 2009
- Bureau C, Poirson H, Péron JM, Vinel JP. Gastroenterol Clin Biol. 2003; 27: 1169-70. [Gabapentine-induced acute hepatitis] French. [PubMed]
- Bureau C, Poirson H, Péron JM, Vinel JP. Gastroenterol Clin Biol. 2003; 27: 1169-70. [Gabapentine-induced acute hepatitis] French. [PubMed]
- Ragucci MV, Cohen JM. Gabapentin-induced hypersensitivity syndrome. *Clin Neuropharmacol*. 2001; 24: 103-5. [PubMed]
- Hamer HM, Morris HH. Successful treatment with gabapentin in the presence of hypersensitivity syndrome to phenytoin and carbamazepine: a report of three cases. *Seizure*. 1999; 8: 190-2. [PubMed]
- Lowe D, Sanvictores T, John S. Alkaline Phosphatase. [Updated 2021 Aug 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK459201/>
- Basith M, Francis A, Bellon A. Reversible thrombocytopenia after gabapentin in an HIV-positive patient. *Case reports in psychiatry*. 2018 Jan 4; 2018.
- LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Gabapentin. [Updated 2020 Jul 30]. Available from: <<https://www.ncbi.nlm.nih.gov/books/NBK548252/>>